REMARKS

IDS Statements

Applicants have filed two Information Disclosure Statements (dated November 29, 2000 and February 12, 2001) in this case. However, the Examiner has not indicated that such statements have been acknowledged. Applicants respectfully request that the Examiner confirm review of such documents by initialing and returning the PTO-1449 forms.

The Rejection of the Claims Under 35 U.S.C. §112, First Paragraph Should Be Withdrawn

Claims 1, 3, 4, 8, 16, and 22 have been rewritten to remove the language "functional equivalents of the ROR receptor". Therefore, any rejection of the claims under §112, first paragraph should be withdrawn.

The Rejection of the Claims Under 35 U.S.C. §112, Second Paragraph Should Be Withdrawn

Claims 1, 3-4, 8, 16, and 22 stand rejected under §112, second paragraph as being allegedly indefinite and unclear for reciting "functional equivalent thereof". These claims have been rewritten without such language.

Claims 3 and 7 has been rewritten to recite "a RNA polymerase", a "yeast nuclear factor Gal4" and a "domain of DEF". No antecedent basis is required for such claim language and therefore any rejection of the claims for lack of antecedent basis should be withdrawn.

The Rejection of the Claims Under 35 U.S.C. §103 Should Be Withdrawn

Claims 1-22 stand rejected under §103(a) as being unpatentable over Wiesenberg et al. ('683) in view of Fraser et al. Applicants respectfully traverse.

Wiesenberg et al. discloses a method for the screening of compounds which can act as ligands to RZR/ROR receptors and which have auto-immune, anti-arthritic, anti-tumor, melatonin-like or melatonin-antagonistic properties. Nowhere does Wiesenberg disclose that his method has applicability for screening compounds which can have use for treating metabolic dysfunction or atherosclerosis. Moreover, Wiesenberg does not disclose or suggest that his method has applicability to expression of the apo C-III gene.

Fraser discloses a method for modulating apo C-III gene expression with the ligand-dependent transcription factor, HNF-4. Specifically, Fraser discloses the effects of modulating HNF-4 transcriptional activity on the endogenous expression levels of the apoAI and apoC-III genes.

In fact, Fraser's disclosure reflects the complexity of the role of nuclear hormone receptors like HNF-4. The family of nuclear hormone receptors is very diverse with members that bind to different DNA response elements and that are expressed in different tissues and that activate or inhibit transcription as discussed in the attached review article by Gronemeyer and Laudet. It is clear that the various members of this family have different physiological functions under the control of ligands of a diverse chemical nature ranging from fatty acid derivatives to steroids or amino acid derivatives. Thus, it is hardly possible to forecast the action of a member of this family on the basis of another family member.

Moreover in the case of the ROR and HNF-4 receptors, these two nuclear receptors have distinct function and spectra of activity. For example, HNF-4 gene deletion is lethal to mice (see attached paper by Chen). However, RORα-deficient mice are viable but display cerebellar defects and bone metabolism alteration. Also, mutations in the HNF-4 gene have been implicated in maturity-onset diabetes of the young, MODY1. (See attached Yamagata et al. paper).. On the basis of this divergent genetic evidence, one of skill in the art would not predict a role of ROR in the metabolism of triglyceride based on the disclosure of Fraser on the HNF-4 effect, and would not be motivated to arrive at the claimed invention.

A further distinction between ROR and HNF-4 can be made on the basis of their DNA binding sequences. HNF-4 binds to a direct repeat of two AGGTCA half-sites separated by one nucleotide ((G/A)G(G/t/a)(T/C/G)(C/t)A(A/g)(A/g)G(G/T)(T/C/G)(C/t)(A/g/c/t)). By contrast, ROR binds to either an AGGTCA halfsite preceded by an AT rich region or to two AGGTCA half-sites separated by two nucleotides and preceded by an AT rich region. Since only a subset of HNF-4

binding sites also possess an AT rich region, one cannot extrapolate a ROR effect from effects of HNF-4 on a given promoter.

Additionally, HNF-4 is critical to the expression of the human apo AI gene (see attached paper by Ginsburg). In figure 13 of the instant application, the inventors provide evidence that RORα does not affect human apo AI promoter activity.

This cumulative evidence clearly points to the remarkable differences between HNF-4 and ROR receptors. One of ordinary skill in the art would not be motivated to activate any given promoter using ROR based on the effects of HNF-4.

In view of this evidence which highlights the significant differences between HNF-4 and ROR, there is clearly no logical nexus which would lead one of skill in the art to combine the teachings of Wiesenberg with the teachings of Fraser to arrive at applicants' instant invention.

Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination. *In re Geiger* (CAFC 1987) 815 F.2d 686, 2 PQ2d 1276.

Therefore, Applicants' invention is not obvious in view of Wiesenberg and Fraser and any rejection based on obviousness should be withdrawn.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached pages are captioned **"Version with Markings to Show Changes Made"**.

In view of the above remarks and amendments, it is submitted that this application is ready for allowance. Early notice to this effect is solicited.

Respectfully submitted,

Robert E. McCarthy (Reg. No. 46,044)
Representative Capacity

Anthony J. Zelano (Reg. No. 27,969)
Attorney for Applicants

MILLEN, WHITE, ZELANO & BRANIGAN, P. C.
Arlington Courthouse Plaza I
2200 Clarendon Boulevard, Suite 1400
Arlington, VA 22201
(703) 812-5322 (Direct dial)
email: mccarthy@mwzb.com

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VERSION WITH MARKINGS TO SHOW CHANGES MADE IN THE CLAIMS

1. **(Twice Amended)** A method of screening a substance for usefulness in the treatment of a lipid metabolism dysfunction comprising contacting said substance with a ROR receptor, or a response element thereof ~~, or a functional equivalent of said receptor or response element,~~ involved in the regulation of the apo C-III gene, and measuring the level of apo C-III gene expression.

3. **(Twice Amended)** A method of screening a substance for usefulness in the treatment of a lipid metabolism dysfunction, comprising contacting said substance with (a) a receptor of the ROR family involved in the regulation of the expression of the apo C-III gene, (b) a response element of the ROR receptor, or (c) a nuclear factor which functionally couples ~~capable of functionally coupling~~ ROR to ~~the~~ a RNA polymerase complex, ~~or (d) a functional equivalent of (a)-(c),~~ and then measuring:

i) the binding of said substance to the ROR receptor ~~or its functional equivalent~~ or the binding of the complex formed by said substance and the ROR receptor to its response element or to a nuclear factor which couples ~~capable of functionally coupling~~ ROR to ~~the~~ a RNA polymerase complex;

or

ii) the modulation of the transcriptional activity of a gene placed under the control of a promoter comprising said response element.

4. **(Twice Amended)** The method of screening according to claim 3, comprising:

a) transfecting a cellular host with a DNA fragment encoding an ROR receptor ~~or one of its functional equivalents~~;

b) cotransfecting the host in a) with a construct comprising a response element of said ROR receptor and at least one reporter gene; and

c) measuring the expression of the reporter gene in the presence of the test substance.

7. **(Twice Amended)** The method of screening according to claim 3, comprising:

a) creating a plasmid which comprises several copies of a response element recognized by a ~~the~~ yeast nuclear factor Gal4 cloned upstream of a strong promoter which controls the activity of a reporter gene;

b) creating a plasmid from a chimera which comprises a ~~the~~ DNA binding domain of Gal4 and a ~~the~~ DEF domain ~~domains~~ of ROR which are the ROR domains to which the ligands bind;

c) cotransfecting the plasmids in a) or b) into a cellular host;

d) incubating the host of c) in the presence of a test substance; and

e) measuring the activity of said reporter gene.

8. **(Twice Amended)** The method of screening according to claim 3, comprising:

a) transforming the cellular host with a construct carrying a gene encoding the ROR receptor ~~or its functional equivalent~~ or a response element of the ROR receptor, and;

b) assaying said cellular host or an extract thereof for the competitive displacement in the binding of labeled and unlabeled ligand to said ROR receptor.

16. **(Twice Amended)** A method for treating or preventing atherosclerosis in humans or animals comprising administering a medicament or a pharmaceutical composition comprising a substance which binds ~~capable of binding~~ to the ROR receptor, or its response element ~~, or a functional equivalent thereof~~ involved in the regulation of the apo C-III gene.

22. (Amended) A method of ~~regulating~~ measuring the expression of the apo C-III gene, comprising contacting a substance with the receptor of the ROR family or a response element of the ROR receptor involved in the regulation of the expression of the apo C-III gene or a response element of the ROR receptor or a nuclear factor which couples ~~capable of functionally coupling~~ ROR to ~~the~~ a RNA polymerase complex, ~~or a functional equivalent thereof,~~ and then measuring:

i) the binding of said substance to the ROR receptor ~~or its functional equivalent~~ or the binding of the complex formed by the said substance and the ROR receptor to its response element or to a nuclear factor ~~capable of functionally coupling~~ which couples ROR to ~~the~~ a RNA polymerase complex;

or

ii) the modulation of the transcriptional activity of a gene placed under the control of a promoter comprising said response element.